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Phenotypic Variation of Autosomal-Dominant Corticobasal Degeneration

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Key Words
Corticobasal degeneration · Progressive supranuclear palsy · Primary progressive aphasia · Tauopathy

Abstract
Neurodegenerative tauopathies may be inherited as autosomal-dominant disorders with variable clinicopathological phenotypes, and causative mutations in the microtubule-associated protein tau (*MAPT*) gene are not regularly seen. Herein, we describe a patient with clinically typical and autopsy-proven corticobasal degeneration (CBD). Her mother was diagnosed to have Parkinson's disease, but autopsy showed CBD pathology as in the index patient. The sister of the index patient had the clinical symptoms of primary progressive aphasia (PPA), but no pathology was available to date. Molecular analysis did not reveal any mutation in the *MAPT* or progranulin (*GRN*) genes. Our findings illustrate that CBD, progressive supranuclear palsy and PPA may be overlapping diseases with a common pathological basis rather than distinct entities. Clinical presentation and course might be determined by additional, yet unknown, genetic modifying factors.

Introduction

Neurodegenerative tauopathies include frontotemporal lobar degeneration (FTLD) and tauopathies with prominent extrapyramidal features like progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and hereditary frontotemporal dementia with Parkinsonism linked to chromosome 17 associated with *tau* gene mutations (FTDP-17*T*) [1–3]. Although distinct clinical and neuropathological criteria have been elaborated which allow differentiation between these disorders, clinical and pathological overlap is frequently seen [4–6]. In addition to FTLD with tau-positive inclusions (FTLD-tau), FTLD may be associated with TDP-43 (TAR DNA-binding protein 43)-positive inclusions (FTLD-TDP), FUS (fused in sarcoma)-positive inclusions (FTLD-FUS), or may be linked to chromosome 3 (FTD-3; FTLD-UPS) [7].

Alternative mRNA splicing of *MAPT* leads to six tau isoforms in the adult human brain, consisting of three tau isoforms with four tandem repeats (4R), and three isoforms with three repeats (3R). In normal adult human brains, similar levels of 3R and 4R tau isoforms are present [8]. The molecular hallmark of neurodegenerative

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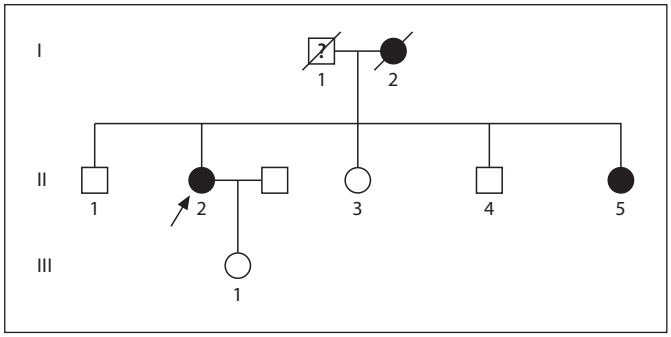

Fig. 1. Pedigree. The arrow indicates the index patient. Circles represent females, and squares represent males. Filled symbols represent affected family members. Open symbols represent clinically unaffected individuals.

tauopathies is the aggregation of particular tau isoforms. In extrapyramidal tauopathies, like PSP, CBD, and a subset of FTDP-17*T* families, aggregation of predominantly 4R tau isoforms was demonstrated, while in others tauopathies filamentous tau aggregates may consist predominantly of 3R (Pick's disease), 4R (argyrophilic grain disease) or a mixture of both, 3R and 4R tau isoforms (subset of FTDP-17*T* cases) [1, 9].

A hereditary 4R extrapyramidal tauopathy caused by *MAPT* mutations was initially described in families with the FTDP-17 phenotype [10]. Later it was recognized that different members of the same kindred with hereditary 4R extrapyramidal tauopathy may exhibit diverse symptoms encompassing the features of FTDP-17, PSP or CBD [6, 11]. In addition, sporadic PSP and CBD share a common MAPT haplotype that increases risk for disease [12, 13]. Therefore, the clinical and pathological phenotypes of hereditary 4R tauopathies may represent different points within one disease spectrum. Since *MAPT* mutations were not regularly found in patients with hereditary tauopathies, additional genetic or epigenetic factors might contribute to the phenotypic diversity.

Here, we describe a family with an autosomal-dominant 4R tauopathy without pathogenic *MAPT* or *GRN* mutation with phenotypic variation, manifesting as CBD, parkinsonism or, presumably, primary progressive aphasia (PPA).

Patients and Methods

The family originates from the German-speaking part of Switzerland (fig. 1). All consenting family members underwent neurological examination, neuropsychological testing and molecular genetic analysis. Extended laboratory analysis, magnetic resonance imaging (MRI), and [^{18}F]-FDG (2-fluoro-2-deoxy-glucose) positron emission tomography (PET) were performed in the index patient and her sister. In addition, available medical records of the deceased family members were studied. Brain autopsy was performed in the index patient (II-2) and paraffin-embedded tissue was available from a former autopsy of her mother (I-2).

Molecular Genetic Analysis

DNA was extracted using standard protocols (QIAamp, QIAGEN, Hilden, Germany). Primer sequences were designed according to GenBank entries and are available on request. PCR amplification was done by a universal 'touch down' protocol, and amplicons were sequenced by fluorescent dye dideoxy terminators on an ABI PRISM® (Applied Biosystems, Forster City, Calif., USA). Exons 1, 7, 9–13 and 16 of the *MAPT* gene, including the flanking intronic regions, were analyzed, thus covering all genomic regions with known mutations. *GRN* sequence analysis was performed as previously described [14].

Neuropathology

Brain autopsy was performed in the index patient. From her mother, paraffin-embedded brain tissue was available for re-evaluation. No brain tissue was available from the index patient's sister.

From the index patient, sections (3 μm) were subjected to conventional stains, including the Gallyas silver technique. Immunohistochemistry was performed with anti-tau antibodies AT8 (phospho-epitopes Ser202 and Thr205; Innogenetics, Ghent, Belgium), RD3 (3R tau isoform; Upstate, Lake Placid, N.Y., USA), RD4 (4R tau isoform; Upstate), alpha-synuclein (human alpha-synuclein; Zymed, San Francisco, Calif., USA), βA4 (human beta-amyloid; DAKO, Glostrup, Denmark), 3F4 (PrP; Signet, Denham, Mass., USA), neurofilament (SMI31; phosphorylated epitopes on the largest neurofilament subunit; Sternberger Monoclonals, Lutherville, Mass., USA), αB-crystallin (Novocastra, Newcastle-upon-Tyne, UK) and glial fibrillary acidic protein (GFAP; Lab Vision Corporation, Newmarket, Suffolk, UK). Sarkosyl-insoluble tau proteins were extracted from the index patient's frontal and temporal cortices, hippocampus, striatum and spinal cord. Western blot analysis, electron microscopy and immuno-electron microscopy were performed as previously described [15]. Micrographs were recorded at a magnification of ×40,000 (Philips EM208S microscope). Dephosphorylation assays were performed as previously described [15].

Results

Case Report of the Index Patient

At 54 years, the right-handed patient (II-2) had difficulties to recognize traffic signs or to relocate her car on a parking lot. During the following months, clumsiness of her left hand developed, and she became unable to work as a beautician. One year later, the first neurological examination at our department revealed psychomotor slowing, left homonymous hemianopsia, marked dysto-

nia of the left arm without spasticity and slight distal weakness (MRC grade M4–5). Muscle tone, strength, and coordination of the right arm and both legs were normal. No involuntary movements were observed. Tendon reflexes were brisk on the left and normal on the right side, plantar responses were flexor. Sensory examination revealed impaired joint position sense on the left side. Cognitive testing demonstrated a right parietal lobe syndrome with neglect, agnosia for affective facial expressions, visuoconstructive deficits, ideomotor apraxia and figural, but not verbal, memory deficits. Language functions were preserved. CSF examination as well as extended laboratory investigations were normal.

Based on the clinical findings, CBD was assumed. Two years after onset, neurological examination revealed marked dystonia of the left arm with almost complete loss of functionality due to dystonia, apraxia, and neglect. The other neurological findings were unchanged and no alien limb phenomenon had developed. Repeated CSF analysis showed strong positivity for protein 14-3-3. Over the following three years, she progressively deteriorated. Dystonia generalized, albeit predominance of the left arm remained, she became wheelchair-dependent and finally bedridden. Five and a half years after onset she suddenly reported severe abdominal pain. Colon perforation was diagnosed and she died 36 h later due to septic peritonitis.

Family Evaluation

The father of the index patient died at the age of 90 years without history of psychiatric or neurological problems. After 61 years, the mother of the index patient developed progressive gait problems, frequent falls, bradykinesia, cognitive deterioration, and swallowing difficulties, and parkinsonism was diagnosed. At the age of 73 years she died due to cardio-respiratory failure. Retrospectively, the predominant gait problems are suggestive of a PSP-like phenotype.

The sister (II-3) of the index patient had progressive word-finding difficulties after 60 years. At 62 years, she demonstrated isolated deficits in language functions, including stagnant spontaneous speech, word-finding difficulties, semantic and phonematic paraphasias, and mild paragrammatism. Reading was slow and stagnant, and there were paralexias of long words. Repetition and writing of dictated long and complex sentences were erroneous. Language comprehension was intact. No deficits in other cognitive functions were identified, and she was diagnosed with PPA.

Table 1. Clinical and molecular characteristics

Proband	Age	Gender	*PRNP* deletion analysis	*PRNP* codon 129	Neurological phenotype	Cognitive abnormalities
I-2	73	f	del/wt	n.a.	Parkinsonian syndrome	n.p.
II-1	59	m	del/wt	M/M	normal	(+)
II-2	57	f	del/del	M/M	CBD	+++
II-3	55	f	del/wt	M/M	PPA	+
II-4	53	m	del/wt	M/V	normal	none
II-5	51	f	del/del	M/M	normal	(+)
III-1	32	f	del/wt	M/M	normal	n.p.

del/wt = Heterozygous 24-bp deletion in the *PRNP* gene; del/del = homozygous 24-bp deletion in the *PRNP* gene; none = no cognitive abnormalities; (+) = slight and probably unspecific cognitive abnormalities; +++ = severe cognitive abnormalities; n.p. = not performed.

The other relatives of the index patient did not report psychiatric or neurological symptoms, and neurological examination was normal. One sibling (II-4) had normal cognitive function. One sibling (II-1) had minimal impairment of verbal retrieval and verbal error checking. Another sibling (II-5) had slight impairment of figural short-term memory (table 1).

Neuroradiology

MRI of the index patient showed bilateral, right-dominant parietal lobe atrophy and symmetrical, periventricular confluating T_2-hyperintense white matter lesions predominantly located in the parieto-occipital regions (fig. 2a, b). FDG-PET demonstrated decreased FDG uptake of the right hemisphere associated with cerebellar diaschisis (fig. 2e, f). Follow-up cerebral MRI documented slight progression of right hemispheric cortical atrophy whereas the leukoencephalopathy remained unchanged (fig. 2c, d). Repeated cerebral FDG-PET suggested a progressive impairment of the right hemispheric glucose metabolism, and increasing cerebellar diaschisis (fig. 2g, h). The sister (II-3) with PPA had normal cerebral FDG-PET. Brain MRI showed diffuse white matter lesions in both hemispheres, predominantly located in frontal and periventricular regions (data not shown).

Molecular Genetic Analysis

None of the examined individuals showed mutations in the genomic regions of the *MAPT* gene with known mutations or in the *GRN* gene. *PRNP* sequence analysis

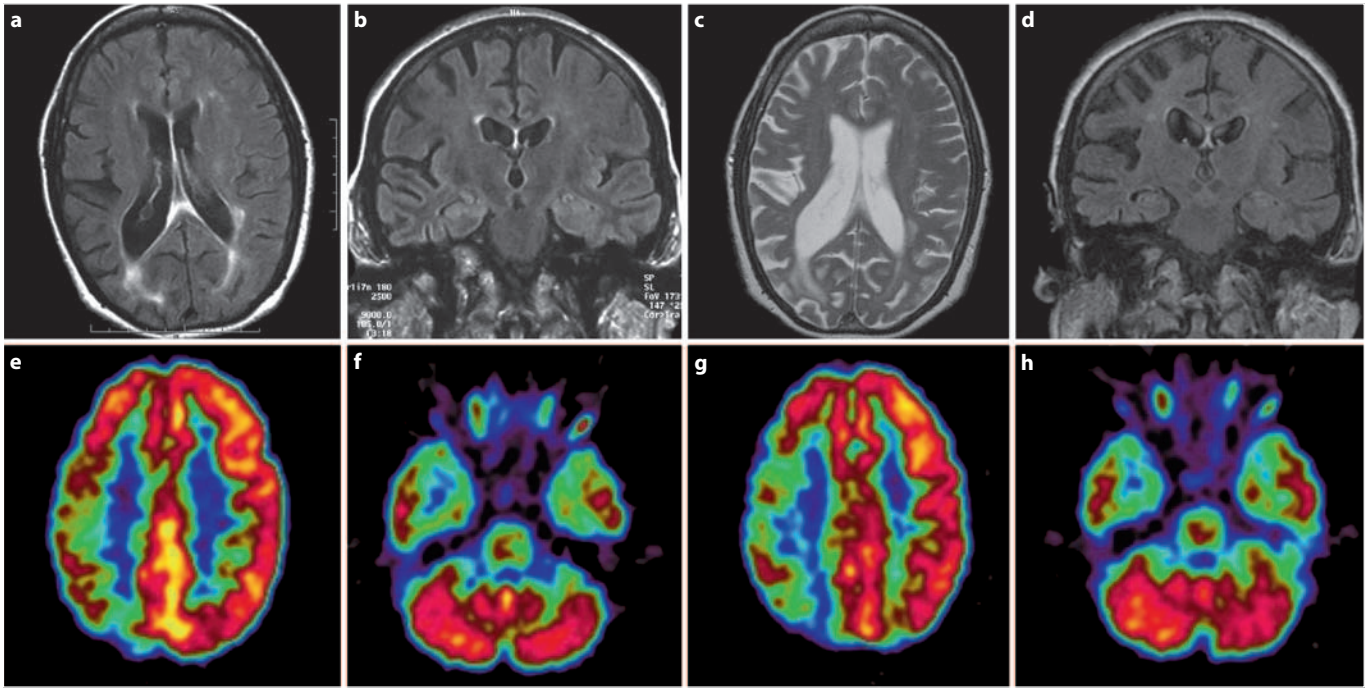

Fig. 2. Imaging. **a** Flair images show hyperintense symmetrical periventricular confluating white matter lesions predominantly located in the parieto-occipital regions, and less prominently in the frontal white matter and the splenium of the corpus callosum. There were no signal abnormalities in basal ganglia and thalamus. **b** Flair images demonstrate right-dominant bilateral parietal lobe atrophy. **c** T2, and **d** flair repeated cerebral MRI 2 years later documents a clear progression of hemispheric cortical atrophy, with unchanged posterior leukencephalopathy. **e**, **f** FDG-PET demonstrates markedly decreased FDG uptake of the right hemisphere. **g**, **h** Repeated cerebral FDG-PET suggest a slightly progressive impairment of the right hemispheric glucose metabolism, and increasing cerebellar diaschisis.

of the index patient (II-2) revealed a homozygous 24-bp deletion in the octapeptide repeat region in the PRNP gene starting at codon 66. Due to the high homology in this region the precise location of the repeat could not be determined. One sibling (II-5) was also homozygous for the 24-bp deletion while all other siblings were heterozygous (table 1). The mother of the index patient was heterozygous. No heterozygous 24-bp deletion in the *PRNP* gene was found in 200 healthy individuals. Individual II-4 was heterozygous for the Met/Val polymorphism at codon 129 whereas the other siblings were homozygous for the Met allele (table 1).

Neuropathology

External examination of the index patient's brain revealed slightly asymmetric cortical atrophy which was most pronounced in the right superior frontal and parietal lobes, while the temporal and occipital lobes were almost spared. Coronal sections revealed thinning of the corpus callosum and enlargement of the lateral and third ventricles. Transverse sections of the brainstem showed pallor of the substantia nigra pars compacta and to a lesser degree of the locus coeruleus.

Histologically, marked neuronal loss, astrocytic gliosis and superficial spongiosis were present in the atrophic cortical regions (fig. 3a). The adjacent subcortical white matter displayed mild to moderate myelin loss and gliosis. In affected cortical areas, mainly in the parietal lobe, scattered ballooned neurons (BN) were noted, immunohistochemically staining for neurofilament, αB-crystallin, and tau antibodies AT8 and RD4 (fig. 3b). Gallyas silver staining, AT8 and RD4 immunohistochemistry revealed numerous astrocytic plaques (fig. 3c). A few astrocytic tau inclusions were reminiscent of tufted astrocytes. Besides BN, cortical neuronal tau pathology was characterized by perinuclear rim-like inclusions, Pick body-like inclusions and some tangle-like inclusions (fig. 3d). Neuronal tau pathology was further noted in basal ganglia, thalamus, substantia nigra and locus caeruleus (fig. 3f). Abundant neuropil threads were noted in affected corti-

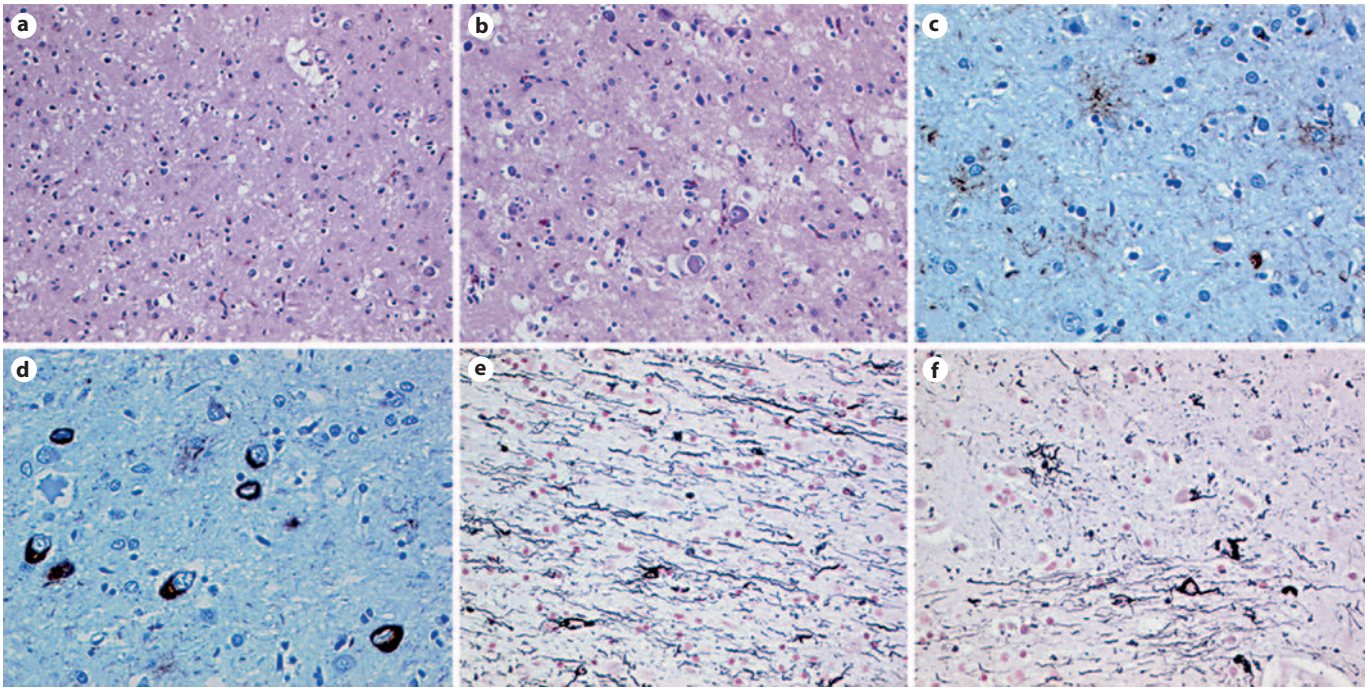

Fig. 3. Brain autopsy findings of the index patient. HE-stained sections of the parietal cortex showing marked neuronal loss, astrogliosis and spongiosis (**a**) together with some ballooned cells (**b**). Cortical AT8 stained astrocytic plaques (**c**) and neuronal tau pathology (**d**). Gallyas silver stain reveals abundant white matter neuropil thread-like structures and coiled bodies (**e**). Gallyas stained thread-like structures in pencil fibers of the striatum in addition to an astrocytic plaque and neuronal tau pathology (**f**). **a** ×100; **b** ×150; **c–f** ×200.

cal and subcortical gray and white matter areas (fig. 3e, f). In white matter areas, there were also numerous coiled bodies. β-Amyloid plaques, neurofibrillary flame-shaped tangles (except few in sector CA2 of the hippocampus), argyrophilic grains as well as Lewy bodies and Lewy neurites were absent (data not shown). Western blot analysis of brain homogenates revealed no PrP^{Sc} (data not shown). Based on these findings, the neuropathological analysis confirmed the clinical diagnosis of CBD.

The diagnosis of CBD was further corroborated by Western blot analysis of sarkosyl-insoluble tau extracted from various regions of the index patient's brain. Antibodies AT8 and AT100 strongly labeled two bands at 68 and 64 kDa (fig. 4b). A slight band at 60 kDa was also observed in the hippocampus of the index patient which is most likely due to the presence of some neurofibrillary tangles found in sector CA2 (see above). By electron microscopy, filaments in the sarkosyl-insoluble tau extracts were labeled with antibody AT8 (fig. 4a). Filaments were predominantly 'narrow twisted ribbons' as reported in other hereditary tauopathies [16]. SDS-PAGE revealed the presence of 3R and 4R tau isoforms in similar ratios indistinguishable from soluble tau extracted from a control brain (fig. 4c). The soluble tau fraction yielded no pattern shift following treatment with lambda-phosphatase, and the bands aligned with all six isoforms of recombinant tau (fig. 4c). In contrast, lambda-phosphatase treatment of sarkosyl-insoluble tau from the temporal cortex of the index patient caused a shift in the band pattern visualized by BR134 and HT7 staining with bands aligning predominantly with 4R recombinant tau isoforms (fig. 4d).

Records from the index patient's mother reported 'brain atrophy' without further specifications. Histologically, mild neuron loss and astrogliosis were found in the striatum while the hippocampus and cerebellum were normal. In the striatum, Gallyas stain and AT8 immunostaining revealed abundant neuropil thread-like processes in the internal capsule, in the pencil fibers, but also in gray matter of the striatum (fig. 5a, b). In the latter, there was neuronal tau-pathology, sometimes shaped as globose neurofibrillary tangles (fig. 5c). Tufted astrocytes were not noted. Tau-pathology was strongly stained with anti-tau antibodies AT8 and RD4 (fig. 5c), but not with antibody RD3 direct against 3R tau isoforms (fig. 5d).

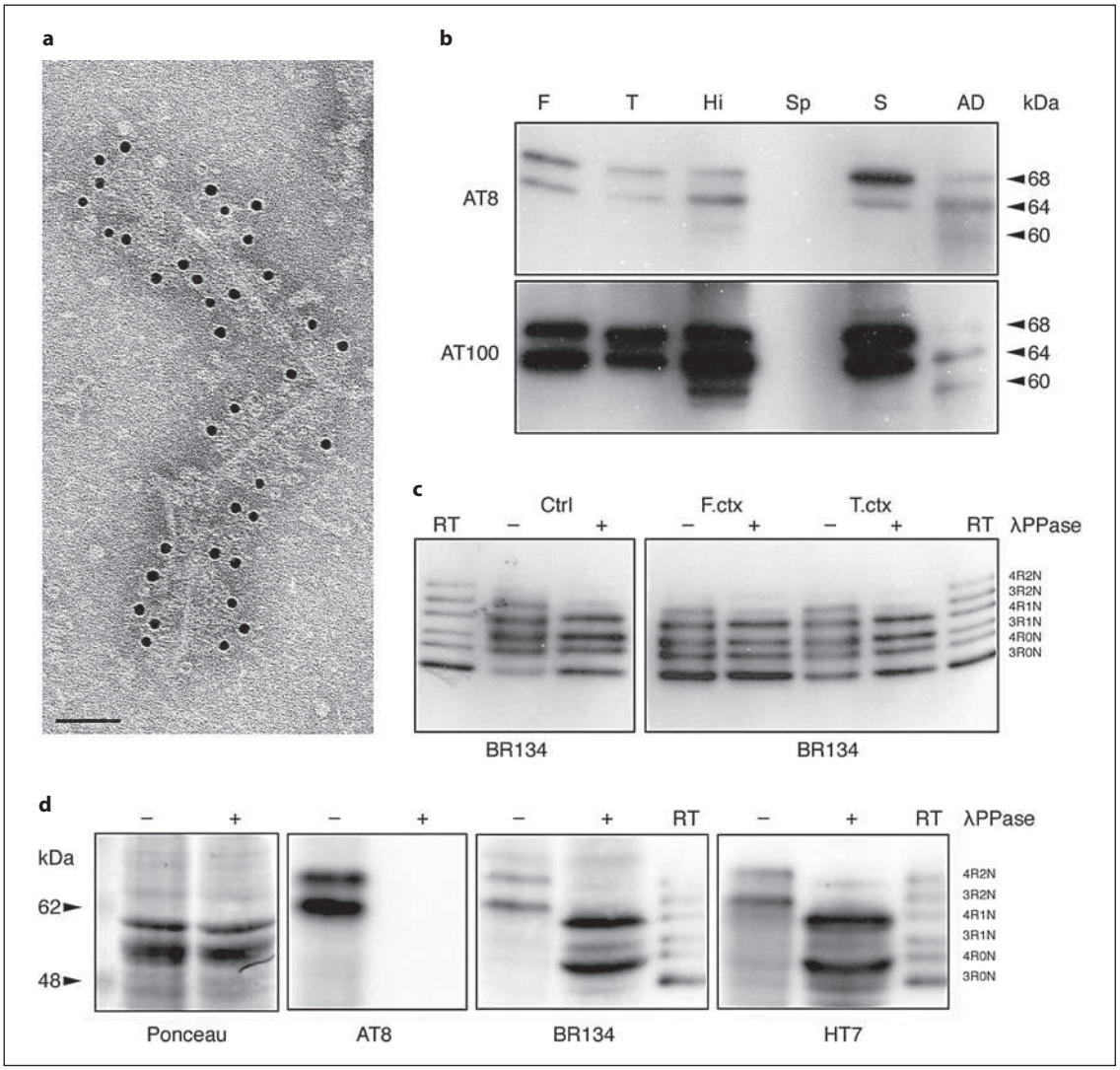

Fig. 4. EM and biochemical analysis of tau pathology of the index patient. **a** Electron micrograph of tau filaments isolated from the sarkosyl-insoluble tau fraction shows labelling with antibody AT8. Scale bar = 100 nm. **b** Immunoblot of sarcosyl-insoluble tau stained with antibodies AT8 and AT100 shows two major bands at 68 and 64 kDa in the frontal (F) and temporal (T) cortex, hippocampus (Hi), and striatum (S) but not in the spinal cord (Sp) which was found to be devoid of tau pathology. The slight tau band at 60 kDa in the hippocampus is likely due to the presence of some paired helical filaments. Immunoblot of PHF-tau extracted from the brain of an Alzheimer patient (AD) shows three major bands at 68, 64 and 60 kDa. **c** BR134 staining reveals similar ratios of 3R and 4R tau isoforms in the heat stable soluble tau fraction of the index patients frontal (F.ctx) and temporal (T.ctx) cortex when compared to a control (Ctrl) brain. No shift is observed after lambda-phosphatase (+) treatment and the bands align with all isoforms of recombinant tau (RT). **d** Sarkosyl-insoluble tau dephosphorylated with lambda-phosphatase (+) and immunoblotted with phosphorylation-independent anti-tau antibodies BR134 and HT7. Two major bands align predominantly with recombinant 4R tau isoforms (4R0N and 4R1N). Immunoblotting with phosphorylation-dependent anti-tau antibody AT8 confirms efficient dephosphorylation of the sample while Ponceau staining shows similar protein loading.

Abundant tau-pathology was further noted in a small strip of the subcortical insular white matter (fig. 5e). In hippocampal sector CA2, several neurofibrillary tangles (NFT) were visualized by Gallyas and AT8 staining (fig. 5f). There were no NFT in other hippocampal sectors and adjacent parahippocampal cortex. Selective neurofibrillary degeneration of hippocampal sector CA2 has recently been described in 4R tauopathies [17]. β-Amyloid plaques, PrP^{Sc} deposits (3F4 immunohistochemistry) and Lewy pathology were absent (data not shown).

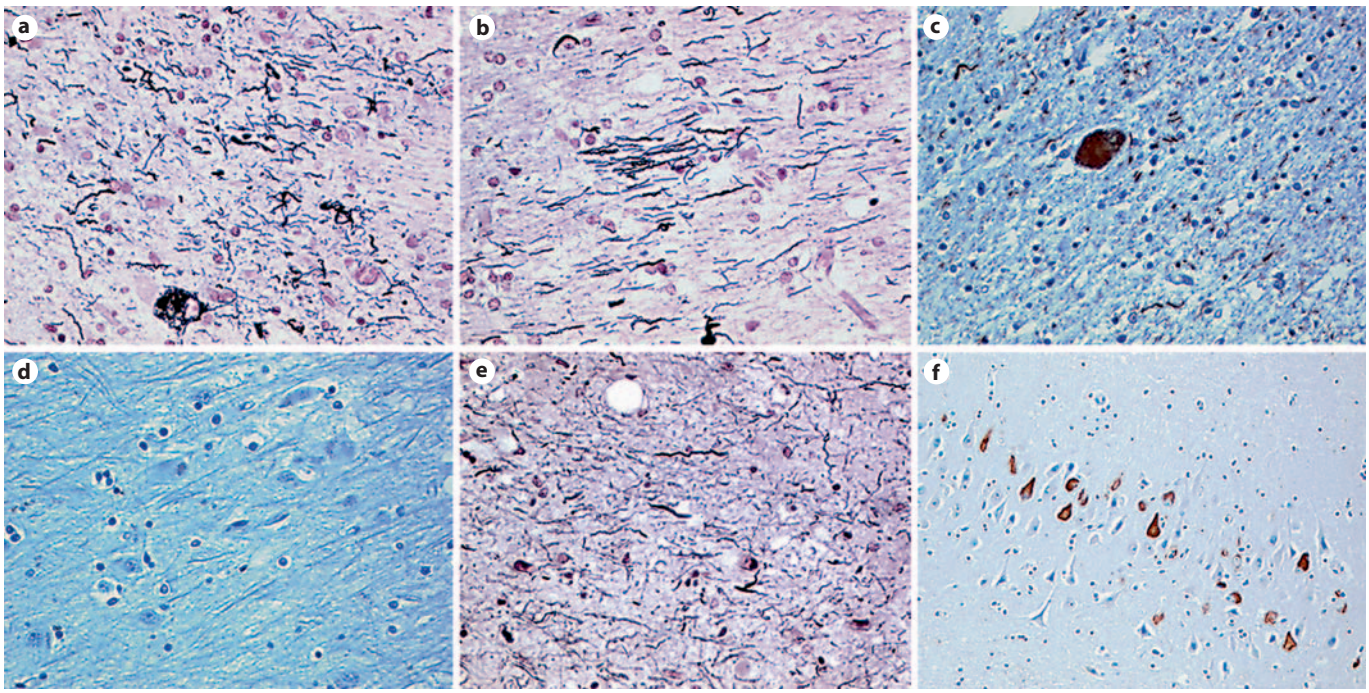

Fig. 5. Histopathological findings of the index patient's mother. Gallyas stain of the striatum shows abundant thread-like structures, neuronal tau pathology and coiled bodies in the gray matter (**a**) as well as in the pencil fibers (**b**). Thread-like structures and a globose tangle stained with anti-tau antibody RD4 recognizing 4R tau isoforms (**c**). Tau pathology is not detected by anti-tau antibody RD3 directed against 3R tau isoforms (**d**). Abundant white matter tau-pathology obtained with Gallyas silver stain (**e**). AT8 stained neurofibrillary tangles in sector CA2 of the hippocampus (**f**). **a–e** ×200; **f** ×100.

Although there were limitations in the pathological investigation of the index patient's mother, histological and immunohistochemical features were strongly suggestive for CBD.

Discussion

The index patient fulfilled the proposed clinical criteria for CBD including asymmetrical rigidity and dystonia nonresponsive to L-dopa with insidious onset and progressive course, signs of cortical dysfunction including apraxia and hemineglect [3, 18]. The neuroradiological findings were in line with this diagnosis, demonstrating progressive asymmetrical cortical atrophy with frontoparietal predominance supported [19]. In the index patient's mother, diagnosis of Parkinson's disease was made. History of progressive gait problems, frequent falls, and bradykinesia suggested a PSP-like phenotype. The histopathological findings, however, confirmed the diagnosis of CBD, thus being compatible with autosomal-dominant inheritance [20]. In both patients, there were no early language deficits such as paraphasias or word-finding difficulties. By contrast, the sister of the index patient (II-3) suffers from PPA without evidence for a movement disorder.

The family pedigree suggests autosomal-dominant inheritance of a neurodegenerative disease presenting as CBD, Parkinsonism (possibly PSP) and PPA. Since no pathological examination is available in the index case's sister with PPA, a different pathologic phenotype such as tau- or TDP-43-positive frontotemporal dementia (FTD) cannot formally be excluded. In the affected family members, we were unable to detect a causative mutation in *MAPT*. Similarly, in other families with hereditary PSP/CBD, mutational screening of the *MAPT* gene revealed no evidence for a pathogenic mutation [11]. Pathogenic *MAPT* mutations were only found in a subset of families with hereditary PSP despite extensive analysis of the *MAPT* gene [21–24]. Although we cannot exclude that a *MAPT* mutation could have been missed by our mutational screening, causative mutations in other genes up- or downstream the tau metabolic pathway might be present. Although mutations in *GRN* are mainly linked to FTLD with TDP-43 pathology, they can also be associ-

ated with CBD and tau-positive cytoplasmatic neuronal inclusions in rare cases [25]. Therefore, we excluded mutations in *GRN* in our index patient. Genetic linkage of familial PSP to an alternative locus on chromosome 1 has recently been demonstrated [24]. Since there were only two informative meioses available in our family, testing for linkage to this locus was not feasible.

The diverse clinicopathological phenotypes of hereditary 4R tauopathies might represent different points on a single disease spectrum and additional genetic or epigenetic factors might contribute to the phenotypic diversity [1, 26–28]. Variable clinical manifestations in families with hereditary tauopathy with *MAPT* mutation P301S as either PSP or CBD have previously been described [29, 30]. CBD is also known to overlap PPA and FTD. Word-finding difficulties and other cognitive deficits are frequent presenting symptoms in CBD [27, 31]. One study investigated patients who presented with PPA or FTD and developed movement disorder/ symptoms of CBD over time. In these patients, the average time between primary manifestation as PPA or FTD and diagnosis of CBD was 2.5 years, including patients who developed CBD 7 years later [32]. Therefore, we cannot exclude that our patient II-3 will develop symptoms of CBD over time.

The high amount of protein 14-3-3 in the CSF of our index patient prompted us to consider *PRNP* as a candidate disease-modifying gene. *PRNP* sequence analysis revealed a homozygous 24-bp deletion in the octapeptide repeat region of the *PRNP* gene. Disease-causing *PRNP* mutations are coding point mutations or integral numbers of octapeptide repeats insertions [33]. The role of deletions in *PRNP* is less clear [33]. Population-based examinations estimated a prevalence of the heterozygous 24-bp deletion of up to 0.5%, which was therefore as a benign polymorphism not predisposing individuals to prion diseases [34].

Nevertheless, it is likely that other yet unidentified genetic modifiers and/or environmental factors are involved in phenotypic variation in our family with hereditary tauopathy.

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